

Linking function to process

F-P links are now being created

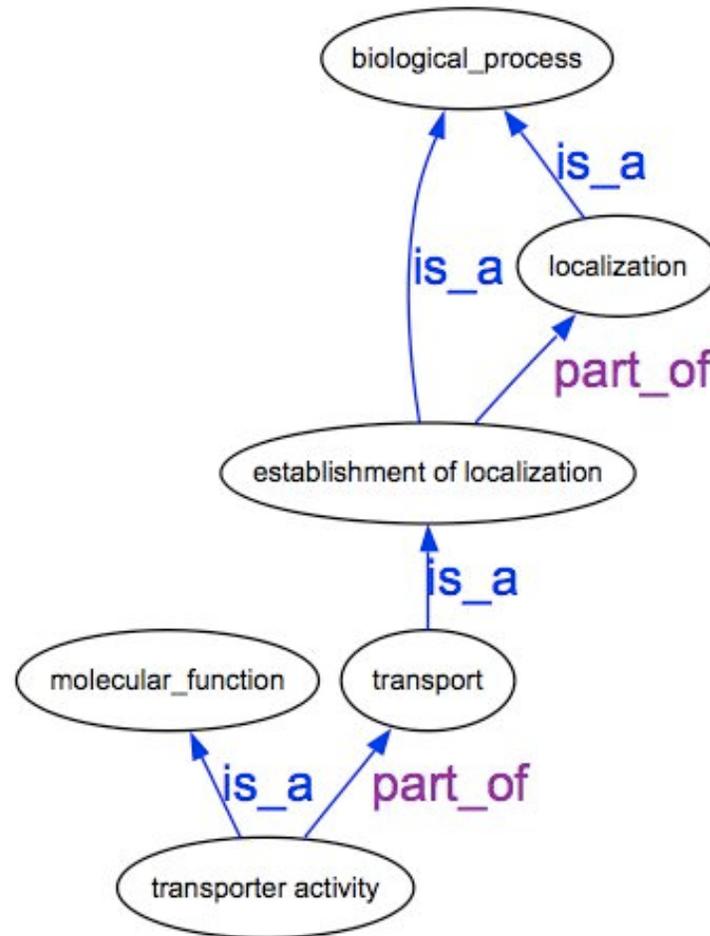
- Intra- and Inter-ontology links
 - GO:
 - Molecular function -> molecular function
 - Regulates
 - is_a
 - part_of
 - Biological process -> biological process
 - Regulates
 - Is_a
 - Part_of
 - Biological process -> molecular function
 - regulates
 - Molecular function -> biological process
 - part_of

Why part_of?

Biological Process; GO:0008150

- Any process specifically pertinent to the functioning of integrated living units: cells, tissues, organs, and organisms. A process is a collection of molecular events with a defined beginning and end.

We have started doing the easy ones



Molecular functions that always occur in a single type of biological process are a part of that biological process.

But it's not as easy as it
appears

We are finding many cases where
function and process are not
parallel.

What does using part_of buy us?

- We sum up annotations specifically in process and include all annotations to the functions that relate to that process.
- Makes it easier for annotators by eliminating a need for coannotation -> more comprehensive annotation
 - Annotators need not annotate to a process if the function is linked to it.

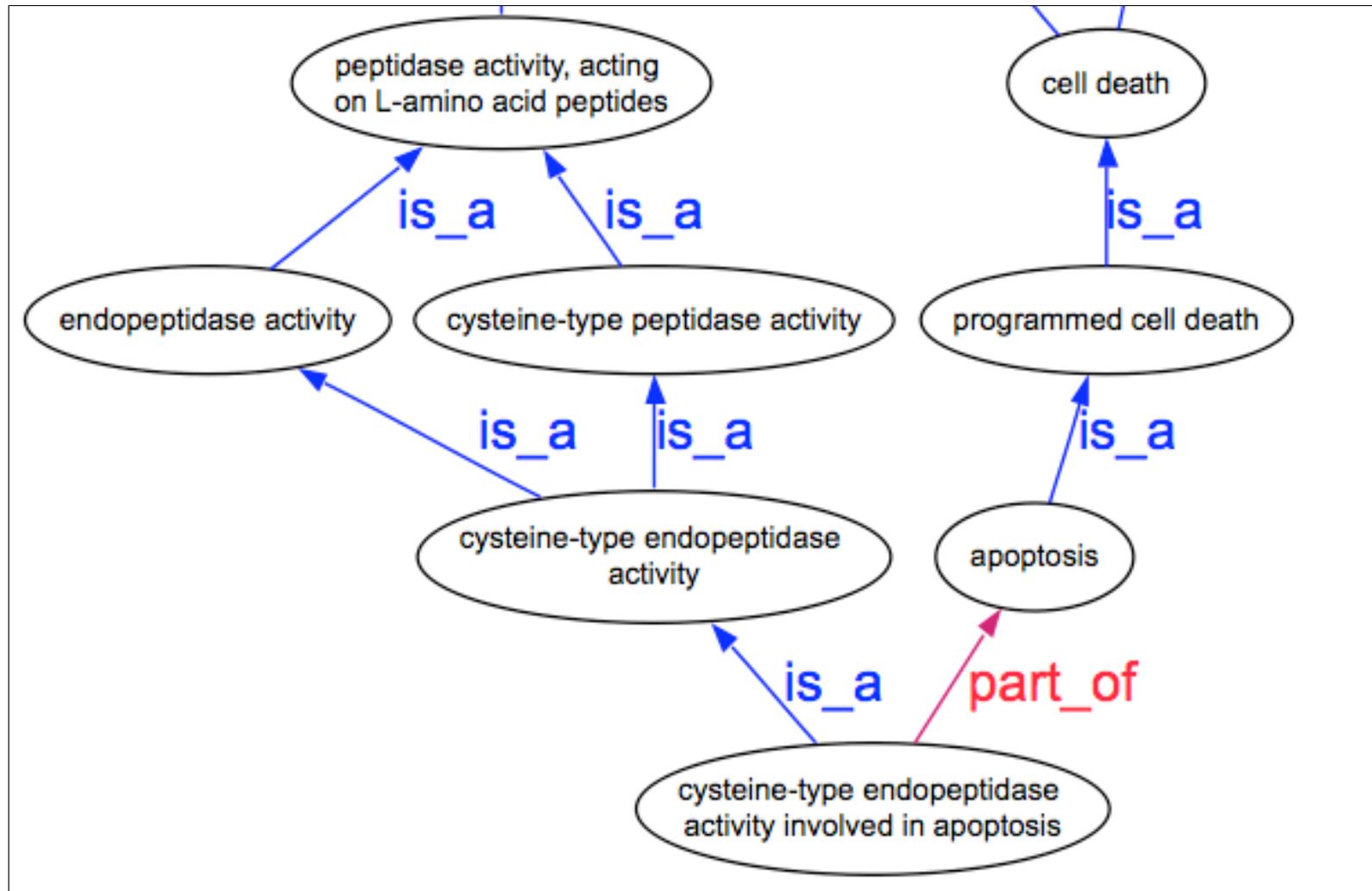
The Future

Process-specific function terms

'caspase activity'

- MF term is obsolete
- 'caspase activator activity' and 'caspase inhibitor activity' terms are NOT

'caspase activity'



Alignment of GO with Pathways Databases

Pilot study with Reactome

Apoptosis in Reactome

The screenshot shows the Reactome website interface. At the top, there is a navigation bar with links like 'Getting Started', 'Latest Headlines', 'GO Browser', etc. Below that is a search bar with the text 'Search for: [] in Homo sapiens [Go!]' and a red banner encouraging users to try the beta version of the interface. The main heading is 'Apoptosis [Homo sapiens]'. On the left, there is a 'Reactionmap' section with a tree view showing 'Apoptosis [Homo sapiens]' expanded to show sub-pathways like 'Extrinsic Pathway for Apoptosis', 'Intrinsic Pathway for Apoptosis', 'Activation of Effector Caspases', 'Apoptotic execution phase', and 'Regulation of Apoptosis'. The main content area is titled 'Apoptosis' and contains a table with metadata and a detailed text description.

Apoptosis	
Stable identifier	REACT_578.2
Authored	Alnemri, E, Hengartner, M, Tschopp, J, Tsujimoto, Y, Hardwick, JM, 2004-01-16
Reviewed	Hengartner, M, Ranganathan, S, Vaux, D
Your feedback	Let us know what you think of this article (click here)
Organism	Homo sapiens
Cellular compartment	cell GO
Represents GO biological process	apoptosis GO Apoptosis [Mus musculus] Apoptosis [Rattus norvegicus]

Apoptosis is a distinct form of cell death that is functionally and morphologically different from necrosis. Nuclear chromatin condensation, cytoplasmic shrinking, dilated endoplasmic reticulum, and membrane blebbing characterize apoptosis in general. Mitochondria remain morphologically unchanged. In 1972 Kerr et al introduced the concept of apoptosis as a distinct form of "cell-death", and the mechanisms of various apoptotic pathways are still being revealed today.

The two principal pathways of apoptosis are (1) the Bcl-2 inhibitable or intrinsic pathway induced by various forms of stress like intracellular damage, developmental cues, and external stimuli and (2) the caspase 8/10 dependent or extrinsic pathway initiated by the engagement of death receptors

The caspase 8/10 dependent or extrinsic pathway is a death receptor mediated mechanism that results in the activation of caspase-8 and caspase-10. Activation of death receptors like Fas/CD95, TNFR1, and the TRAIL receptor is promoted by the TNF family of ligands including FASL (APO1L OR CD95L), TNF, LT-alpha, LT-beta, CD40L, LIGHT, RANKL, BLYS/BAFF, and APO2L/TRAIL. These ligands are released in response to microbial infection, or as part of the cellular, humoral immunity responses during the formation of lymphoid organs, activation of dendritic cells, stimulation or survival of T, B, and natural killer (NK) cells, cytotoxic response to viral infection or oncogenic transformation.

The Bcl-2 inhibitable or intrinsic pathway of apoptosis is a stress-inducible process, and acts through the activation of caspase-9 via Apaf-1 and cytochrome c. The rupture of the mitochondrial membrane, a rapid process involving some of the Bcl-2 family proteins, releases these molecules into the cytoplasm. Examples of cellular processes that may induce the intrinsic pathway in response to various damage signals include: auto reactivity in lymphocytes, cytokine deprivation, calcium flux or cellular damage by cytotoxic drugs like taxol, deprivation of nutrients like glucose and growth factors like EGF, anoikis, transactivation of target genes by tumor suppressors including p53.

In many non-immune cells, death signals initiated by the extrinsic pathway are amplified by connections to the intrinsic pathway. The connecting link appears to be the truncated BID (tBID) protein a proteolytic cleavage product mediated by caspase-8 or other enzymes. [Kerr 2002, Kerr et al 1972, MacFarlane & Williams 2004, Cory et al 2003, Adams 2003, Ashkenazi 2002, Cory & Adams 2002]

Apoptosis in Reactome

Reactome: Caspase mediated cleavage of APC

http://www.reactome.org/cgi-bin/eventbrowser?DB=gk_current&FOCUS_SPECIES=Homo%20sapiens&ID=202947&

Getting Started Latest Headlines GO Browser Adult_AD Theiler choice SO PDFs References Query evidence code Production cell_type SourceForge.net: Gen... CVS Repository PubMed Home

Diagram

Details

open to selected event open all close all

- Apoptosis
 - Extrinsic Pathway for Apoptosis
 - Intrinsic Pathway for Apoptosis
 - Activation of Effector Caspases
 - Apoptotic execution phase
 - Apoptotic cleavage of cellular proteins
 - Caspase-mediated cleavage of cytoskeletal proteins
 - Apoptotic cleavage of cell adhesion proteins
 - Breakdown of the nuclear lamina
 - Caspase mediated cleavage of APC**
 - Caspase mediated cleavage of C-IAP1
 - Caspase-mediated cleavage of FADK1
 - Caspase 3-mediated cleavage of PKC theta
 - Caspase-mediated cleavage of PKC theta
 - Caspase-mediated cleavage of Acinus
 - Caspase-mediated cleavage of Rock-1
 - Caspase-mediated cleavage of farnesyl transferase
 - Caspase mediated cleavage of BAP31
 - Caspase-mediated cleavage of Etk
 - Caspase-mediated cleavage of MAMK1

Caspase mediated cleavage of APC	
Stable identifier	REACT_12012.1
Authored	Schulze-Osthoff, K, 2007-09-03
Reviewed	Ranganathan, S, 2007-11-23
Your feedback	Let us know what you think of this article (click here)
Cleavage of APC by caspase 3 and release of the amino-terminal fragment (1-760) are required for the APC mediated acceleration of apoptosis-associated caspase activity (Qian et al., 2007). [Qian et al 2007]	
Input (present at start of reaction)	APC [cytosol]
Output (present at end of reaction)	APC fragment (1-777) [cytosol] APC fragment (778-2843) [cytosol]
Catalyst	active caspase-3 [cytosol]
GO molecular function	cysteine-type endopeptidase activity GO
Preceding event(s)	Cleavage of Procaspase-3 by the apoptosome [Homo sapiens] Dissociation of Caspase-3 from SMAC:XIAP:Caspase-3 [Homo sapiens]
Organism	Homo sapiens
Cellular compartment	cytosol GO
References	Webb, SJ, Nicholson, D, Bubb, VJ, Wylie, AH <i>Caspase-mediated cleavage of APC results in an amino-terminal fragment with an intact armadillo repeat domain</i> 1999 FASEB J PubMed

Done

Of course GO is different from
a representation of the
organism-specific pathways

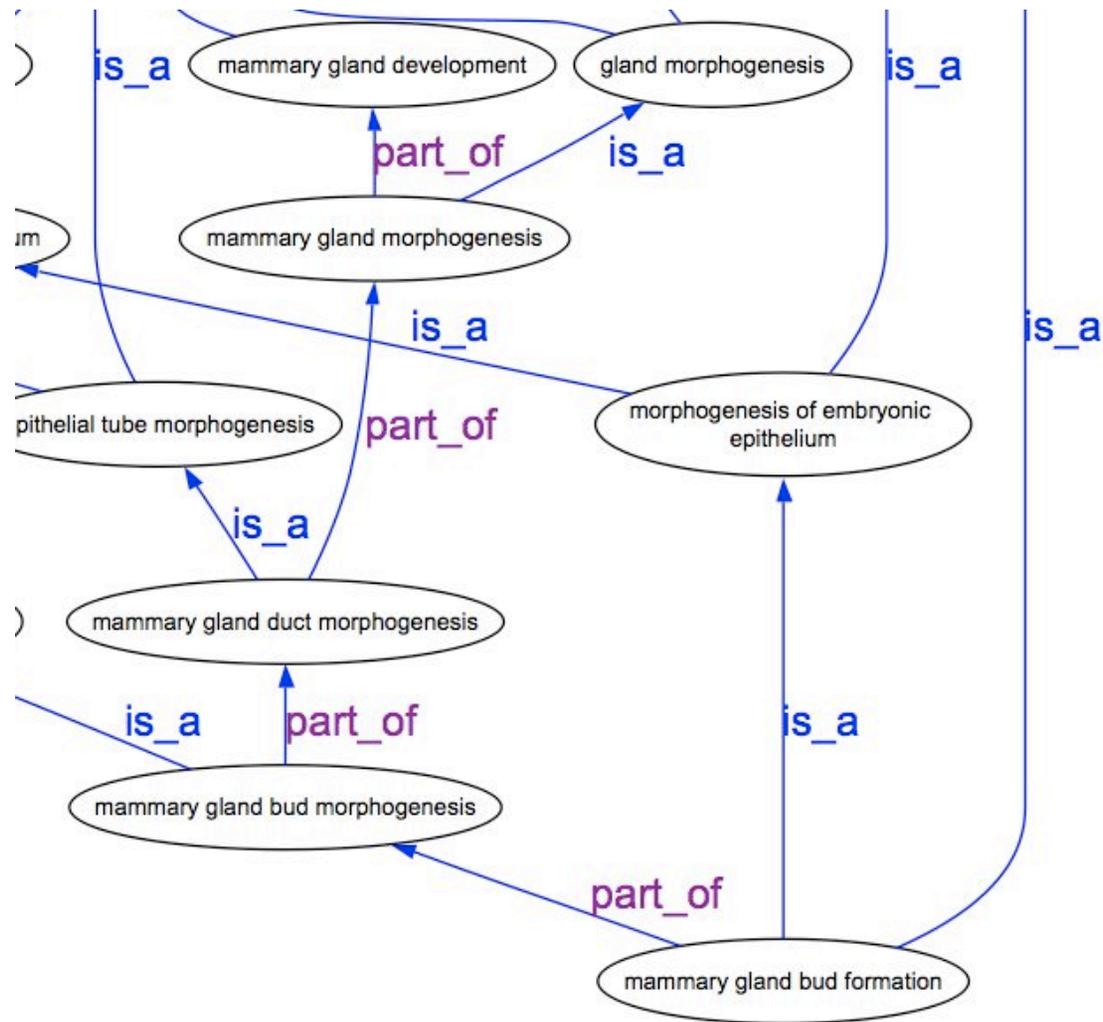
- The 'Cyc's
- KEGG
- Panther
- PW

What do process-specific functions buy us?

- We can build hypotheses.
- If GP X has MF A
- And subtypes of MFA are linked to BP 1, 2, and 3
- Then X could be involved in BP1, 2, and/or 3.
- We can bring in data from other sources (expression data, phenotype) to figure out which BP it might be and can test that.

What I want to do

What signaling pathways might contribute to mammary gland development?



What I want to do

What signaling pathways might contribute to mammary gland development?

[mammary gland bud formation ; GO:0060615](#) [\[show def\]](#) [\[view in tree\]](#)

	Symbol, full name	Information	Qualifier	Evidence	Reference	Assigned by
<input type="checkbox"/>	Fgf10 fibroblast growth factor 10	63 associations BLAST gene from <i>Mus musculus</i>		IMP With MGI:MGI:1859647	MGI:MGI:2155478	MGI
<input type="checkbox"/>	Fgf10 fibroblast growth factor 10	60 associations BLAST gene from <i>Rattus norvegicus</i>		ISO With RGD:10578	RGD:1624291	RGD
<input type="checkbox"/>	Fgfr2 fibroblast growth factor receptor 2	47 associations BLAST gene from <i>Mus musculus</i>		IMP With MGI:MGI:2153811	MGI:MGI:2155478	MGI
<input type="checkbox"/>	Fgfr2 fibroblast growth factor receptor 2	55 associations BLAST gene from <i>Rattus norvegicus</i>		ISO With RGD:10581	RGD:1624291	RGD

What I want to do

What signaling pathways might contribute to mammary gland development?

Fgf10

<input type="checkbox"/>	GO:0042056 : chemoattractant activity	15 gene products view in tree	molecular function	IDA	MGI:MGI:3609523	MGI
				IDA	MGI:MGI:3611702	MGI
<input type="checkbox"/>	GO:0005104 : fibroblast growth factor receptor binding	21 gene products view in tree	molecular function	IDA	MGI:MGI:3687933	UniProtKB (via MGI)
<input type="checkbox"/>	GO:0008083 : growth factor activity	184 gene products view in tree	molecular function	IDA	MGI:MGI:3687933	UniProtKB (via MGI)
<input type="checkbox"/>	GO:0008201 : heparin binding	159 gene products view in tree	molecular function	IDA	MGI:MGI:3687933	UniProtKB (via MGI)

Fgfr2

<input type="checkbox"/>	GO:0017134 : fibroblast growth factor binding	19 gene products view in tree	molecular function	IPI With RGD:735698	RGD:632663	RGD
				ISO With RGD:10581	RGD:1624291	RGD
				IPI With RGD:69203	RGD:2289853	RGD
<input type="checkbox"/>	GO:0005007 : fibroblast growth factor receptor activity	16 gene products view in tree	molecular function	IPI With RGD:735698	RGD:632663	RGD
				TAS	RGD:632663	RGD

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Fgf10

<input type="checkbox"/>	GO:0042056 : chemoattractant activity	15 gene products view in tree	molecular function	IDA	MGI:MGI:3609523 MGI
<input type="checkbox"/>	GO:0005104 : fibroblast growth factor receptor binding	21 gene products view in tree	molecular function	IDA	MGI:MGI:3611702 MGI
<input type="checkbox"/>	GO:0008083 : growth factor activity	184 gene products view in tree	molecular function		
<input type="checkbox"/>	GO:0008201 : heparin binding	159 gene products view in tree	molecular function		

fibroblast growth factor receptor signaling pathway

Fgfr2

<input type="checkbox"/>	GO:0017134 : fibroblast growth factor binding	19 gene products view in tree	molecular function	IPI With RGD:735698	
				ISO With RGD:10581	RGD:1624291 RGD
				IPI With RGD:69203	RGD:2289853 RGD
<input type="checkbox"/>	GO:0005007 : fibroblast growth factor receptor activity	16 gene products view in tree	molecular function	IPI With RGD:735698	RGD:632663 RGD
				TAS	RGD:632663 RGD